In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 14-1056V

(Filed: November 25, 2020)

AMANDA L ISAACSON,	*	To Be Published
Petitioner,	*	Ruling on Entitlement; Influenza ("Flu") Vaccine; Rapid Progressive Glomerulonephritis ("RPGN"); Progressive Glomerulonephritis with Monoclonal IgG Deposits ("PGNMID")
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Scott Taylor, Esq., Urban and Taylor, S.C., Milwaukee, WI, for petitioner.
Darryl Wishard, Esq., U. S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On October 29, 2014, Amanda Isaacson ("Ms. Isaacson," or "petitioner") timely filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, et seq.[2] (the "Vaccine Act" or "Program"), alleging that an influenza ("flu") vaccination she received on November 3, 2011 caused her to develop glomerular nephritis.[3] Petition at 1-2.

[1] This Ruling has been designated "to be published," which means I am directing it to be posted on the Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). **This means the Ruling will be available to anyone with access to the internet.** However, the parties may object to the Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Ruling will be available to the public. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] Petitioner initially included a claim that she suffered from Postural Orthostatic Tachycardia Syndrome ("POTS"). Petitioner filed an expert report from Dr. Younger, a neurologist, and supporting medical literature. Pet. Ex. 15-16, ECF No. 22; Pet. Ex. 17-18, ECF No. 23; Pet. Ex. 19, ECF No. 24. Following a

An entitlement hearing was held on January 24 and 25, 2019, in Washington, D.C. For the reasons stated herein, I find that petitioner's evidence is sufficient to demonstrate that the flu vaccine she received on November 3, 2011 more likely than not caused her development of glomerular nephritis. Accordingly, I find that petitioner is entitled to compensation.

I. Issues to be Determined

The parties agree that petitioner received a flu shot on November 3, 2011; she was subsequently diagnosed with glomerulonephritis ("GN") with monoclonal IgG deposits within days of the vaccination; and she experienced sequelae of her GN for more than six months. Joint Sub. at 1. The parties disagree that the flu vaccine can cause GN with monoclonal IgG deposits, that it did so in this case, and/or that petitioner developed GN within a medically appropriate timeframe following her flu vaccination to support causation. *Id*. at 1-2. Respondent submits that petitioner had a "pre-existing, chronic, and underlying but silent nephrotic condition that coincidentally manifested after her flu vaccination." *Id*. at 1. Petitioner did not advance a claim that the flu vaccine she received significantly aggravated a preexisting kidney disease. *Id*.

II. Background

A. Procedural History

Petitioner filed her petition ("Pet.") on October 29, 2014 and filed medical records through January of 2015. *See* Pet., ECF No. 1; Petitioner's Exhibits ("Pet. Ex.") 1-10, ECF No. 7; Pet. Ex. 11, ECF No. 8; Pet. Ex. 12-13, ECF No. 12. On February 6, 2015, respondent filed a Rule 4(c) Report ("Rule 4") stating that compensation was not appropriate. ECF No. 13. On July 14, 2015, petitioner filed an affidavit from her treating physician, Dr. Carey. Pet. Ex. 14, ECF No. 18.

This case was reassigned to me on January 14, 2016. ECF No. 27.

On March 1, 2016, respondent filed an expert report from Dr. Low, a neurologist, and supporting medical literature. Resp. Ex. A-B, ECF No. 29; Resp. Ex. C-K, ECF No. 30. On March 2, 2016, respondent filed an expert report from Dr. Kaplan, a nephrologist, and supporting medical literature. Resp. Ex. L-P, ECF No. 31.

Following a status conference on March 30, 2016, petitioner was ordered to file an expert report from a nephrologist by May 31, 2016. Scheduling Order at 1, ECF No. 32. Petitioner was also ordered to submit a settlement demand to respondent within 15 days of filing her expert report. *Id*. at 2.

Following four extensions of time, petitioner filed an expert report from a nephrologist, Dr. Kielstein, along with supporting medical literature, on January 31, 2017. Motion for Extension of Time ("MFET"), ECF No. 34; Second MFET, ECF No. 35; Third MFET, ECF No. 36; Fourth MFET, ECF No. 37; Pet. Ex. 21-38, ECF No. 38. Petitioner was ordered to file a status report

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status conference on October 5, 2017 and discussion regarding petitioner's claim for POTS, petitioner filed a status report on December 4, 2017 formally advising she would not be pursuing her claim for POTS. *See* Scheduling Order, ECF No. 48; Pet. S.R., ECF No. 50.

confirming that a settlement demand had been submitted to respondent by February 15, 2017. Non-PDF Order, issued Jan. 31, 2017. On February 14, 2017, petitioner filed a status report requesting until March 31, 2017, to submit a settlement demand to respondent. ECF No. 39. The deadline for petitioner to submit a settlement demand was extended accordingly. Non-PDF Order, issued Feb. 14, 2017. Petitioner filed a status report ("Pet. S.R.") on April 3, 2017, three days after the deadline, requesting additional time to submit a settlement demand. Pet. S.R., ECF No. 40. The deadline was extended to April 14, 2017. Non-PDF Order, issued Apr. 3, 2017. Petitioner failed to comply with the Court's order.

A status conference was held on April 26, 2017. Petitioner requested thirty days to file updated medical records and a status report confirming that a settlement demand had been submitted to respondent. A deadline was set for May 26, 2017. Scheduling Order, ECF No. 41.

On July 4, 2017, respondent filed a status report ("Resp. S.R.") advising he was no longer interested in settlement, along with a responsive expert report from Dr. Kaplan. Resp. S.R., ECF No. 46; Resp. Ex. Q, ECF No. 47.

Petitioner filed a supplemental expert report from Dr. Kielstein on January 4, 2018. Pet. Ex. 41, ECF No. 51.

A Rule 5 conference was held on February 27, 2018. Scheduling Order, ECF No. 53. I noted that respondent's expert, Dr. Kaplan, opined that petitioner suffered from a preexisting silent kidney disease and ongoing chronic process. *Id*. at 2. I asked petitioner whether she would like to amend the petition to include a claim for significant aggravation. *Id*. Petitioner did not file an amended petition.

A prehearing order was issued on April 27, 2018, setting this matter for an entitlement hearing on January 24 and 25, 2019 in Washington, D.C. Prehearing Order, ECF No. 59.

Petitioner filed her pre-hearing brief on November 29, 2018. ECF No. 60. Respondent filed his pre-hearing brief on December 10, 2018. ECF No. 63.

An entitlement hearing was held in Washington, D.C. on January 24 and 25, 2019. Following the hearing, petitioner filed demonstrative exhibits used by Dr. Kielstein, and respondent filed an updated CV for Dr. Kaplan. *See* Pet. Ex. 50-51, ECF No. 76; Resp. Ex. V, ECF No. 77.

The parties filed their post hearing briefs on June 14, 2019. ECF Nos. 88-89.

This matter is now ripe for decision.

B. Medical History

1. Petitioner's Health Before Receiving the Flu Vaccine

Petitioner was born on April 21, 1985. Pet. Ex. 47 at 9. Her prior medical history included migraines since the age of 11 or 12, tension headaches, and skin rashes. *Id*. at 13, 18. She also suffered from neck and back pain associated with an automobile accident in August of 2006. *Id*.

In 2009, petitioner reported bladder infections about every six months but was otherwise healthy. Pet. Ex. 47 at 9. She had a family history of hypertension, hyperlipidemia, lung cancer, migraines, and fibromyalgia. *Id*. at 13; Pet. Ex. 48 at 27. An MRI of her head was ordered following a headache for seven days and was unremarkable but for chronic sinus infections. Pet. Ex. 47 at 27.

Petitioner presented for routine examinations over the years, at which time blood work and urine testing were performed. Her laboratory results were generally normal. *See generally* Pet. Ex. 47; Pet. Ex. 50.

In 2010, petitioner underwent sinuplasty and septoplasty for deviated septum and recurring sinus infections. Pet. Ex. 47 at 61-62, 64. She also underwent routine care for pregnancy with her first child, who was born on December 12, 2010 without event. *See generally* Pet. Ex. 48. She received an influenza vaccine in October of 2010 without event. Pet. Ex. 47 at 211.

2. Petitioner's Health After Receiving the Flu Vaccine

Petitioner is a nurse and received the allegedly causal influenza vaccine on November 3, 2011 while at work. Pet. Ex. 1 at 1.

Five days later, on November 8, 2011, petitioner presented to the ER at Oconomowoc Memorial Hospital ("OMH") complaining of fever, headache, neck and back pain, chills, myalgias, sweats, and vomiting ongoing for two days. Pet. Ex. 2 at 8. She did not have cough, diarrhea, or an upper respiratory infection. *Id*. She was diagnosed with renal insufficiency, dehydration, and a urinary tract infection. *Id*. at 11. She tested negative for strep. Pet. Ex. 12 at 1. She was given IV fluids, an antibiotic and discharged. Pet. Ex. 2 at 10-11.

On November 10, 2011, petitioner returned to the ER in renal failure with hematuria. Pet. Ex. 2 at 101-07. Her visit two days prior in which she had an elevated creatinine[4] level of 3.0 that decreased to 2.7 after four liters of fluid was noted. *Id*. at 103. She was still not feeling well. *Id*. at 104. She was drinking fluids and "putting out a good amount of urine." *Id*. Urine culture on this date came back positive for *E. coli* with an elevated creatinine level at 3.7, and BUN[5] of 30. *Id*.

[4] Creatinine level is used to measure renal function. *See Mosby's Manual of Diagnostic and Laboratory Tests* 171 (Pagana eds., 6th ed. 2018) [hereinafter "*Mosby's*"]. An increased creatinine level indicates a disease affecting renal function, such as glomerulonephritis. *Id*. at 172. A normal creatinine level for a woman between 18 and 41 years old is 0.5 to 1.0 mg/dL; a creatinine level greater than 4.0 mg/dL indicates a serious impairment in renal function. *Id*. at 171.

[5] "BUN," or blood urea nitrogen, is an indirect measurement of renal function and glomerular filtration rate. *Mosby's* at 453-54. The BUN/creatinine ratio is a good measurement of kidney and liver function. *Id*. at 454. A normal adult range is 6 to 25. *Id*.

She was admitted for further management and reversal of renal insufficiency. *Id*. at 104-05, 372-73.

A kidney biopsy performed revealed crescentic glomerulonephritis, immune complex-type. Pet. Ex. 2 at 531. "[T]his patient has a diffuse extracapillary proliferative glomerulonephritis (crescentic glomerulonephritis). The presence of IgG Kappa predominance by IF is suggestive of a new glomerular entity termed proliferative glomerulonephritis monoclonal IgG Kappa." *Id*. The biopsy revealed the presence of two fragments of renal cortex containing nine glomeruli,[6] two of which were globally sclerotic.[7] *Id*. Five non-globally sclerotic glomeruli contained fresh and cellular crescents, almost all of which were circumferential and associated with some breaks in the glomerular basement membrane. *Id*. at 531-32. There was necrosis[8] of one glomerular tuft and two glomeruli showed segmental sclerosis. *Id*. at 532. Massive protein droplets were seen in the residual proximal tubules.[9] *Id*. There was acute tubular necrosis[10] with infiltration of polys around several of the tubules.[11] *Id*. Many tubules contained red blood cells. *Id*. Hydropic degeneration[12] was noted within the proximal tubules. *Id*. There was 4+ diffuse interstitial[13] inflammation by reactive lymphocytes.[14] *Id*. No vasculitis[15] was identified in the section studied. *Id*. Predominant

[6] "Glomeruli" is the plural of glomerulus; the glomerular tuft is formed by capillaries in the kidney and is the site of the filtration barrier between the blood and the kidney. *Glomeruli*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 778 (33d ed. 2020) [hereinafter "DORLAND'S"]. at 777; *glomerulus*, DORLAND'S at 778.

[7] Sclerosis is hardening of a tissue. *Sclerosis*, DORLAND'S at 1652.

[8] "Necrosis" means physical changes indicative of cell death, caused by progressive degradation action of enzymes. *Necrosis*, DORLAND'S at 1218.

[9] A tubule is one of the minute, reabsorptive, secretory, and collecting canals, made up of basement membrane, that form much of the parenchyma of a kidney. *Tubulus renalis*, DORLAND'S at 1953-54.

[10] Acute tubular necrosis is acute renal failure with mild to severe damage or necrosis of tubule cells. *Acute tubular necrosis*, DORLAND'S at 1218.

[11] "Poly" is the colloquial name for a polymorphonuclear leukocyte, a type of white blood cell. *Poly*, DORLAND'S at 1463; *leukocyte*, DORLAND'S at 1015.

[12] Hydropic degeneration is the swelling of cells caused by accumulation of intracellular water in response to cell injury. *Hydropic degeneration*, DORLAND'S at 474.

[13] Interstitial tissue, or connective tissue, binds together and supports the various structures in the body. *Interstitial tissue*, STEDMAN'S MEDICAL DICTIONARY 922360, accessed via westlaw.com (last visited Oct. 9, 2020) [hereinafter STEDMAN'S]; *connective tissue*, DORLAND'S at 1901.

[14] A lymphocyte is a type of white blood cell. *Lymphocyte*, DORLAND'S at 1070; *leukocyte*, DORLAND'S at 1015.

[15] Vasculitis is inflammation of a blood or lymph vessel. *Vasculitis*, DORLAND'S at 1996.

findings were IgG, C3, and Kappa 3-4+ staining in the mesangial[16] and capillary walls. *Id*. IgA, IgM, C4, C1q, albumin, and fibrinogen[17] were all negative and Lambda[18] had much less staining at 12+ compared to Kappa. *Id*.

Based on the foregoing renal biopsy result, petitioner was diagnosed with acute renal failure, characterized as acute proliferative crescentic glomerulonephritis, also known as rapidly progressive glomerulonephritis ("RPGN") by renal biopsy.[19] Pet. Ex. 2 at 105-07. She was treated with plasmapheresis and prednisolone. *Id*. Petitioner required only three of the planned five treatments due to her rapid improvement. *Id*. at 107. She developed sinus bradycardia after the second round of plasmapheresis. *Id*. at 101. At discharge on November 17, 2011, her treating nephrologist, Dr. Carey, listed petitioner's diagnosis as acute renal failure, confirmed as acute proliferative crescentic glomerulonephritis, sinus bradycardia, and volume overload. *Id*. at 105-06. Dr. Carey further noted, "It is believed that since the patient got her influenza vaccination which actually prompted her trips to the ER for nausea and emesis, the flu vaccine may have been the stimulus for the rapidly progressive crescenteric GN." *Id*. at 107. Another of petitioner's treaters, Dr. Taft, noted, "This is a young lady who is experiencing any (sic) glomerulonephritis following an influenza vaccine. Temporally, the two have to be related." *Id*. at 138.

Petitioner presented to her gynecologist on November 30, 2011. She advised that she needed to go back on birth control due to severe renal problems and the need for steroids and other medication. Pet. Ex. 48 at 4.

Two months later, on January 20, 2012, petitioner presented to OMH following eight days of nausea and new-onset vomiting. Pet. Ex. 2 at 550-51. She was admitted due to a concern for neurocardiogenic abnormality. *Id*. at 556. She was discharged on January 22, 2012, with a normal echocardiogram, mild gastritis, and a headache believed to be related to prednisone, for which Fioricet was prescribed. *Id*. at 559-62. She had mild orthostatic symptoms and Dr. Carey instructed her to wean prednisone as quickly as possible.[20] *Id*.

Petitioner continued her nephrology care with Dr. Carey. *See generally* Pet. Ex. 4. Petitioner gave birth to her second child, a healthy baby girl, on July 3, 2013. *See generally* Pet.

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[16] "Mesangial" means pertaining to the mesangium, the thin membrane that helps support the capillary loops in the renal glomerulus. *Mesangium*, DORLAND'S at 1122.

[17] "Fibrinogen" is factor I, a type of coagulation factor. *Fibrinogen*, DORLAND'S at 694. Coagulation factors are substances in the blood that are essential to the clotting process. *Coagulation factors*, DORLAND'S at 667.

[18] "Lambda" refers to a type of light chain found in immunoglobulin molecules. *Lambda chain*, DORLAND'S at 330.

[19] RPGN is an acute form of glomerulonephritis marked by a rapid progression to end-stage renal disease and, histologically, by profuse epithelial proliferation, often with epithelial crescents; principal signs are proteinuria, hematuria, and anemia. *Rapidly progressive glomerulonephritis*, DORLAND'S at 778.

[20] As petitioner no longer alleges that she suffers from POTS as a result of the flu vaccine, the medical records regarding treatment for POTS are not included in this summary.

Ex. 6; Pet. Ex. 10.

Over four years later, on January 31, 2016, petitioner was admitted to OMH with a relapse of crescentic glomerulonephritis. Pet. Ex. 40 at 382. She presented with a two-day history of fever, chills, body aches, and nausea attributed to a "viral GI bug her daughter had a few days prior." *Id*. She had a fever of 100.4 degrees, with labs remarkable for a white blood cell ("WBC") count of 17.67. *Id*. Urinalysis revealed blood, ketones, protein and some WBCs, "though chronically, she has blood and protein in her urine." *Id*. Rocephin was started and she was admitted for sepsis. *Id*. A renal biopsy was performed on February 3, 2016 which showed 14 glomeruli, four of which were globally sclerotic, and five crescents. *Id*. at 550. Two other glomeruli showed focal necrotizing areas. *Id*. There was moderate tubular atrophy and mild interstitial fibrosis involving about 15% of the interstitial compartment. *Id*. at 551. Overall, the biopsy was "consistent with the crescentic form of proliferative glomerulonephritis with monoclonal IgG deposits…This would represent a recurrence." *Id*. at 550. "It was felt that her viral illness triggered this episode of GN." *Id*. at 382. She was started on high-dose Solumedrol and transferred to Waukesha Memorial Hospital for initiation of plasmapheresis and Cytoxan. *Id*. Antibiotics were discontinued. *Id*.

Thereafter, Dr. Carey referred petitioner to the Mayo Clinic for evaluation. Pet. Ex. 20. Following a full history and examination at the Mayo Clinic, Dr. Green's impression was "immunosuppression responsive disease" reduced by re-initiation of immunosuppressive therapy. Pet. Ex. 20 at 5. Petitioner had "steroid-induced cushingoid[21] appearance" and was slightly anemic. *Id*. She was on chronic Cytoxan therapy. *Id*. A nephropathology report dated April 21, 2016 compared petitioner's biopsies from November 2011 and February 2016 and concluded that she had proliferative glomerulonephritis with monoclonal IgG kappa deposits with necrotizing and crescentic activity and minimal chronicity. *Id*. at 11-12. Dr. Greene wrote, "It is difficult to know specifically if the vaccine and/or related issues caused her acute crescentic GN. It is certainly within the realm of possibility with acute antibody formation. I will discuss with some of our colleagues in Infectious Disease to determine how much of a potential reaction has been reported with the influenza vaccine as a cause of kidney disease." *Id*. at 5.

C. Affidavit and Testimony of Amanda Isaacson

Petitioner is a registered nurse who previously worked triage. At the time of the hearing, she worked at a behavioral health facility as the manager of infection control and wellness. Tr. 7-8. She is married with two children. Tr. 6, 14.

On November 3, 2011, when petitioner received the flu vaccine, she had no health concerns. Tr. 8-9. She had occasional UTIs but did not have hypertension or any other conditions. Tr. 9.

Three days after the flu vaccine, on November 6, 2011, petitioner described onset of headache, body aches, and typical viral symptoms. Tr. 10; Pet. Ex. 3 at 1. She affirmed her

[21] "Cushingoid" means resembling the features, symptoms, and signs associated with Cushing syndrome. *Cushingoid*, DORLAND'S at 444. Symptoms of Cushing syndrome include fat deposits on the face, neck, and trunk, dusky complexion with purple striae, and muscular wasting and weakness. *Cushing syndrome*, DORLAND'S at 1797.

symptoms progressed; the next day, she developed severe chills and neck pain, "[a]nd as a triage nurse, I know that's a very big concern." Tr. 10-11. She stated she had flu-like symptoms before, but never anything that made her stay in bed or home from work. Tr. 11.

Petitioner presented to the emergency room on November 8, 2011 and was diagnosed with a urinary tract infection and increased creatinine levels. Pet. Ex. 3 at 2. She returned on November 10, 2011 and was admitted. *Id*. She was treated by Dr. Carey, a nephrologist, who ordered a renal biopsy, which showed acute crescentic glomerulonephritis. *Id*. As a result, she remained in the hospital until November 17, 2011. *Id*.

Petitioner affirmed that she continued to follow up with Dr. Carey over the next few months so that he could monitor her renal function. Pet. Ex. 3 at 3.[22]

Petitioner stated in January of 2016, she presented to the ER with symptoms similar to those in November of 2011. Tr. 12. "[S]o it started with a headache and nausea, just as it previously had done. Symptoms continued to worsen over the next two days, again, starting with fever, chills, body aches to where I was in bed all day." Tr. 12. Once in the hospital, she was tested for flu and other viruses, and it was determined to be a relapse of RPGN. Tr. 12. Petitioner affirmed that she continues to suffer from complications associated with renal failure and glomerulonephritis, which she was informed are permanent. Pet. Ex. 3 at 6.

Petitioner confirmed receipt of flu vaccinations in 2009 and 2010, without event. Tr. 13-14. She has not received a flu vaccine since November 3, 2011. Tr. 14. Both her nephrologist, Dr. Carey, and her primary care physician have advised her not to receive any further vaccinations. Tr. 15. "Dr. Carey determined that my kidney related conditions were caused by the administration of the [flu] vaccination on [November 3, 2011]." Pet. Ex. 3 at 6.

D. Affidavit of Dr. Mark Carey

Dr. Mark Carey is a board-certified nephrologist and is petitioner's treating doctor since her presentation with renal failure on November 10, 2011. Pet. Ex. 14 at 1-2. Dr. Carey affirmed, in his opinion, petitioner "suffered an acute and rapidly progressive proliferative crescentic glomerulonephritis" and that "the administration of the influenza vaccination on November 3, 2011 triggered [petitioner's] glomerulonephritis condition…." *Id*. at 8. He further affirmed that petitioner suffers from residual effects or complications from the glomerulonephritis since the date of the administration of the vaccination and although she is in remission, she has suffered permanent kidney damage as a result of the acute onset of this disease. *Id*. Dr. Carey added that she "will not be able to receive vaccinations due to the potential harm they pose given her damaged kidneys." *Id*.

Dr. Carey affirmed that "it is more likely than not" the influenza vaccine caused petitioner's glomerulonephritis. Pet. Ex. 14 at 8-9. He further affirmed that "[i]t has been accepted that after vaccinations," the risk of immune response related diseases increases. *Id*. at 9. For example, influenza vaccine is widely known as a risk for peripheral nerve disorders such as Guillain-Barré

[22] The portion of petitioner's affidavit concerning POTS is not being included since petitioner did not pursue that claim.

syndrome ("GBS"), which is an autoimmune condition related to acquired heightened antibody-mediated humoral immunity. *Id.*[23] Dr. Carey posited that the flu vaccination led to an acquired heightened immunity in petitioner, similar to GBS, as a result of exposure to either inactivated vaccine viral particles or the preservative in the vaccine. *Id*. This led to petitioner's development of crescentic glomerulonephritis. *Id*. In Dr. Carey's opinion, the time between petitioner's vaccination and the onset of her injury conformed to the usual pattern for post-vaccination reactions. *Id*. Dr. Carey affirmed that he considered alternative reasons for the sudden onset of petitioner's symptoms but could find no reasonable alternative causation for petitioner's crescentic glomerulonephritis. *Id*. at 10.

III. The Retained Experts

A. Petitioner's Expert, Dr. Jan Kielstein

Dr. Kielstein is a nephrologist who is board certified in internal medicine and nephrology in Germany. Pet. Ex. 21 at 2; Tr. 16. He is the director of the Department of Nephrology, Hypertension, and Blood Purification at the Academic Teaching Hospital in Braunschweig, Germany, where he treats the whole spectrum of nephrological diseases, with the exception of immediate post-kidney transplant patients. *Id*. Dr. Kielstein is also an Associate Professor of Medicine at the Hanover Medical School in Hanover, Germany, a subspecialty editor for acute kidney injury in *Nephrology Dialysis and Transplantation*, and a member of the Board of Trustees of the International Society for Apheresis. *Id*. He is scientifically active, as evidenced by over 247 peer reviewed publications listed in the U.S. National Library of Medicine. *Id*.

At the time of hearing, Dr. Kielstein was working at a 1500-bed tertiary care hospital. Tr. 17. He explained tertiary care as the highest level of medical/clinical service in the hospital. Tr. 17. "So we start where other hospitals give up." Tr. 17. It is also a teaching hospital; he teaches medical student in their last year of medical school, as well as residents and fellows. Tr. 17-18.

Dr. Kielstein was involved in one other case in the Vaccine Program, after which he began "investigating the effect of flu vaccine on renal kidney injury markers." Tr. 18. He began asking patients presenting with acute renal illness if they had vaccinations prior to their acute illnesses. Tr. 18. As a result, "we have published two cases in which there is a temporal[,] and in my view, pathophysiological possible relationship between the vaccine and the onset of the renal disease. And I think that interest kind of qualified me to be here." Tr. 19.

B. Respondent's Expert, Dr. Bernard Kaplan

Dr. Kaplan was a pediatric nephrologist. He retired two years prior to this hearing. Tr. 85. Dr. Kaplan was the Chief of Pediatric Nephrology at The Montreal Children's Hospital from 1980 to 1987 and subsequently at The Children's Hospital of Philadelphia ("CHOP") from 1987 to 2010. Resp. Ex. L at 1. From 2010 until his retirement, he was an attending pediatric nephrologist at CHOP. *Id*. Dr. Kaplan is currently an emeritus professor at the University of Pennsylvania in the department of pediatrics and an emeritus nephrologist at CHOP. Tr. 85. He is board-certified in

[23] *See* Helmar C. Lehmann et al., *Guillain-Barre Syndrome After Exposure to Influenza Virus*, 10 LANCET INFECT. DIS. 643-51 (2010), filed as "Resp. Ex. O."

pediatrics and pediatric nephrology. Resp. Ex. L at 1. He has published papers and chapters on the subject of glomerulonephritis and has co-edited a textbook in which this condition is discussed, PEDIATRIC NEPHROLOGY AND UROLOGY: THE REQUISITES IN PEDIATRICS (1st ed., 2005). *Id*. Dr. Kaplan has a total of 50 years of involvement with treating patients with glomerulonephritis and glomerular disorders. *Id*.; Tr. 93. At hearing, Dr. Kaplan shared that the proudest accomplishments during a medical career are theories and/or hypotheses that, with time, develop into a connection with injury or disease. He discussed several examples of this phenomenon in his own career, including a connection between indomethacin and kidney disease, as well as the pathogenesis of IgA nephropathy. Tr. 87-93, 105-06. Dr. Kaplan's life's work deals with the discoveries of circulating antigens from medications and/or diseases in the body infiltrating the kidney and causing GN, noting the importance of reporting case studies which can grow into connections being made.

Dr. Kaplan has testified in Vaccine Program cases three or four times and has written two or three additional opinions. He has testified for both defendant and plaintiff in medical malpractice cases. Tr. 93, 150-51.

IV. Applicable Law

A. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. 42 U.S.C. § 300aa-11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352 (Fed. Cir. 1999).[24] Petitioners are not required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs*., 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioner does not bear the burden of eliminating alternative independent potential causes"). Once a petitioner has proven causation by preponderant evidence, "the burden then shifts to the respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs*., 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing 42 U.S.C. § 300aa-13(a)(1)(B)).

[24] The Vaccine Act also requires petitioners to show by preponderant evidence that the "residual effects or complications" of the alleged vaccine-related injury lasted for more than six months. § 11(c)(1)(D)(i). It is undisputed that this six-month requirement is satisfied in this case.

To prove causation, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id*. at 1278. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. Under the first *Althen* prong, petitioner must provide a "reputable medical theory" demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id*. at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341.

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). Even if the vaccination can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs*., 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *id*. at 961 (citation omitted), and "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury," *Paluck v. Sec'y of Health & Human Servs*., 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375).

However, medical records and/or statements of a treating physician's view do not per se bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 12(b)(1)(providing that "[a]ny such diagnosis, conclusion, judgment, test result, report or summary shall not be binding on the special master or court."); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009)("there is nothing…that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the

reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 742, 749 (2011) (determining it is not arbitrary or capricious for a special master to weigh competing treating physicians' conclusions against each other), *aff'd*. 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 Fed. Appx. 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 229, 2011), *mot. for review den'd*, 100 Fed. Cl. 344 (Sept. 29, 2011), *aff'd*, 475 Fed. Appx. 765 (Fed. Cir. 2012).

The third *Althen* prong requires that petitioner establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id*. However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id*.; *see also Locane v. Sec'y of Health & Human Servs*., 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

B. Evaluating Expert Testimony

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1991).[25] *Cedillo v. Sec'y of Health & Human Servs*., 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs*., 195 F.3d. 1302, 1316 (Fed. Cir. 1999)).

The *Daubert* factors are usually employed by judges in the performance of their evidentiary gatekeeper roles to exclude evidence that is unreliable and/or could confuse the jury. In Vaccine Program cases, by contrast, these factors are used in the weighing of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness of expert testimony has routinely been upheld. *See, e.g., Snyder*, 88 Fed. Cl. at 742-45. In this case, as in numerous other

[25] The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

Vaccine Program cases, *Daubert* has not been employed to determine what evidence should be admitted, but rather to determine whether expert testimony offered is reliable and/or persuasive.

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion, "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1325-26 (Fed. Cir. 2010) ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act.").

C. Consideration of Medical Literature

Finally, although this decision discusses many but not all the literature in detail which was submitted by the parties, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs*., 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Human Servs*., 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. Appx. 982 (Fed. Cir. 2015).

V. Analysis

A. Overview of acute proliferative crescentic glomerulonephritis with monoclonal IgG deposits ("PGNMID") and rapidly progressive glomerulonephritis ("RPGN")[26]

Dr. Kielstein explained that "glomerulonephritis" is a general term used to describe injury to the glomeruli. It is also the heading for many different injuries to the kidney, including PGNMID, proliferative immune complex-mediated GN, post-infectious GN, immune-mediated GN, and RPGN. Tr. 22. All these conditions are forms of "glomerulonephritis" but the conditions themselves are not interchangeable. Tr. 22.

[26] At the beginning of the hearing, it was agreed that RPGN would be used throughout the hearing to refer to petitioner's injury; however, as citations to the transcript will show, that did not end up being the case.

Dr. Kaplan defined RPGN as "any glomerular disease characterized by extensive crescents (usually involving more than 50% of the glomeruli) as the main histological finding and correlated clinically by a rapid loss of renal function (usually a 50% decline in the GFR within 3 months)." Resp. Ex. L at 4.

Dr. Kielstein went further, describing RPGN as "the renal equivalent of breaking the dam." Tr. 21. According to Dr. Kielstein, blood vessels in the part of the kidney called the glomerular tuft are normally "tight and sealed, and they only permit certain substances of fluid to move" through a barrier. In RPGN, the barrier in the glomerulus suffers severe damage and is broken. As a result, blood components pour into that space "and you get accumulation of a lot of different things in a very confined space. This is building up and kind of compressing the vessels in the glomerulus and it's a sign of severe renal damage." Tr. 21. Clinical signs of RPGN include severe and rapid deterioration of renal function with red blood cells in the urine, edema, and hypertension. Tr. 21-22.

Dr. Kielstein further explained that RPGN has many causes and, because it is an antibody-mediated disease, it can be caused by any disease that causes antibodies to attack the kidney. Tr. 23. For example, Goodpasture syndrome occurs when antibodies attack a very well-defined and specific part of the glomerular basement membrane, the alpha-3 chain of type IV collagen, and destroy the membrane and glomerular barrier function. Tr. 23-24. In lupus, immune complexes[27] form in the glomerular basement membrane, causing disruption to the membrane. Tr. 24. Pauci-immune GN is an antineutrophil cytoplasmic antibody-associated vasculitis ("ANCA" or "AAV") where damage is done, not by immune complexes or antibodies, but by neutrophils or monocytes that "have gone wild." Tr. 24. About one percent of RPGN cases are idiopathic, where known causes are excluded but no known underlying cause is found. Tr. 24, 81.

Dr. Kielstein explained that in immune-complex GNs, the immune complexes are deposited in the glomerulus, where they bind complement[28] and initiate an inflammatory process; this attracts neutrophils and macrophages and results in an alteration to the basement layer of the kidney. *Immune-complex glomerulonephritis*, STEDMAN'S at 375400. The difference between immune complexes, which are the crystallization point of the injury, and a more specific immune complex, like Pauci-immune GN, is the stimulant. Tr. 27-28. In Pauci-immune GN and C-ANCAs, the stimulant is neutrophils, but in other immune complex GNs, the stimulant is cytokines and eosinophils. Tr. 27-28. In RPGN, there is no single cause, but rather combinations of immune complexes. Tr. 28. Monoclonal IgG is a type of immune complex; however, in contrast to "classical" immune complexes, monoclonal IgG also involves the complement system. Tr. 27.

Dr. Kielstein relied on Nasr et al., who first described PGNMID in 2004. The name PGNMID was assigned to 10 cases that did not fit the criteria for other kidney conditions. Pet. Ex.

[27] An immune complex is an antigen combined with a specific antibody. *Immune complex*, STEDMAN'S at 194290.

[28] The complement system is a group of more than 20 proteins which can participate in a cascade, resulting in cell lysis. *Complement system*, STEDMAN'S at 892750.

26 at 2;[29] *see also* Resp. Ex. T at 1[30] (Noting that the same authors described recurrent PGNMID in patients two years post-kidney transplant). In these 10 cases, 100% of patients presented with proteinuria, 80% with renal insufficiency, 60% with microhematuria, and 50% with monoclonal or urine protein. *Id*. at 1, 5; *see also* Pet. Ex. 27 at 2 (summarizing the findings of the 2004 Nasr study).

Further, Dr. Kielstein offered that Nasr distinguished PGNMID from other forms of immune complex-mediated GN previously described, noting that the latter "are due to localization in glomeruli of antibodies complexed to endogenous or exogenous antigens" while "[t]he absence of underlying infectious, autoimmune, or other systemic disease in the vast majority of patients" with newly observed PGNMID suggested "that monoclonal IgG is deposited as a free, noncomplexed Ig that has the ability to aggregate to form definable electron dense deposits." Pet. Ex. 27 at 6-8; Resp. Ex. N at 6-7.

The Nasr study concluded with respect to PGNMID:

> [W]e propose that this unique glomerulonephritis may arise in the course of normal immune responses. It is possible that during an immune response (to extrinsic or intrinsic antigens), one or more clones of B cells proliferate and produce monoclonal IgG molecule (particularly IgG3) with ability to self-aggregate and rapidly deposit in glomeruli through entrapment and/or interaction with negatively charged glomerular constituents…The possibility of an oligoclonal response with the same IgG light- and heavy-chain isotype cannot be excluded because monoclonality can be proved only by immunoblotting/immunofixation techniques.

Pet. Ex. 27 at 8; Resp. Ex. N at 7.

Additionally, Dr. Kielstein relied on a 2017 case report of two patients with PGNMID which noted, although the etiology of PGNMID is not well known, cases have been associated with hematological and infectious causes. Resp. Ex. T at 4. The pathogenesis, outcome, and management of PGNMID remain controversial. *Id*. However, treatment with immunosuppressive agents seems to be effective. Pet. Ex. 27 at 7.

B. Petitioner Has Carried Her Burden of Proof

Application of the *Althen* prongs reveals evidence in support for petitioner's claim: (1) petitioner offered a persuasive medical theory; (2) the theory provided is applicable to the facts of petitioner's case; and (3) petitioner has established a medically acceptable timeframe in which her symptoms could have begun or developed.

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[29] Samih H. Nasr et al., *Proliferative Glomerulonephritis with Monoclonal IgG Deposits: A Distinct Entity Mimicking Immune-Complex Glomerulonephritis*, 65 KIDNEY INT. 85-96 (2004), filed as "Pet. Ex. 26."

[30] Basma Mehri et al., *Proliferative Glomerulonephritis with Monoclonal IgG Deposits in Two Kidney Allografts Successfully Treated with Rituximab*, 10 CLIN. KIDNEY J. 405-10 (2017), filed as "Resp. Ex. T."

1. Petitioner Has Articulated a Sound and Reliable Medical Theory Connecting the Flu Vaccine to the Onset of RPGN/PGNMID.

To satisfy *Althen* Prong I, petitioner must present a "sound and reliable medical or scientific explanation" causally connecting the vaccine to her alleged injuries. *Knudsen,* 35 F.3d at 548.

Dr. Kielstein opined that because the influenza vaccine causes the body to produce both IgG antibodies and cytokines, which can act in concert to damage the glomerular basement member, the influenza vaccine can trigger RPGN/PGNMID. Tr. 31.

Dr. Kielstein's theory relies on the studies conducted by Nasr as described above, and specifically in Nasr's proposition that PGNMID may arise in the course of a normal immune response to an antigen, where B cells produce monoclonal IgG molecules that self-aggregate and rapidly deposit in glomeruli. *See* Tr. 74; Pet. Ex. 21 at 8-9, quoting Pet. Ex. 27 at 8.

Dr. Kielstein explained that the flu vaccine causes the immune system to produce IgG antibodies which build up rapidly in the body. Studies have shown that "patients have a very high and measurable IgG response" within seven days of vaccination. Tr. 29-30. Similarly, the flu vaccine induces a cytokine response by the immune system. Tr. 30. These cytokines, including interferon gamma and several types of interleukins, also build up rapidly, within three to seven hours post-vaccination. Tr. 30. Interferon gamma and IgG are "both components…that are relevant to the pathophysiology of an RPGN." Tr. 30. The IgG antibodies can cause damage to the glomerular basement membrane and the capillaries; this damage can be exacerbated by interferon gamma. Tr. 31. The severity of RPGN increases with elevated interferon gamma levels. Tr. 31.

Further, Dr. Kielstein explained, through the same process that influenza virus can cause PGNMID, the flu vaccine can cause PGNMID. "The influenza antigen and vaccine proteins share substantial structural similarity, which raises the possibility that the influenza vaccine can activate the same autoimmune mechanisms that are activated by infectious antigens." Pet. Ex. 22 at 3.[31] This concept is known as molecular mimicry, an antigen-specific phenomenon involving "activation of autoreactive B and T cells due to antigen similarity between the host antigen and microbial antigen." *Id*. Infection-related signals can trigger innate immunity, which "enhances the immunogenicity of host antigens and may play a role in overcoming the regulatory pathways that limit the autoimmune response." *Id*. The vaccine could provide "a transient inflammatory setting for bystander activation resulting in release of previously sequestered self-antigens or stimulating an innate response." *Id*. Dr. Kielstein referred to the association between the flu vaccine and GBS as an example of molecular mimicry between the flu vaccine and host tissue. *Id*.

Dr. Kielstein explained how the viral RNA contained in the flu vaccine can trigger the immune system to "target" the kidneys. Tr. 31-32. The "components of bacteria and viruses can trigger an immune response resulting in an immune complex glomerulonephritis." Tr. 32. The flu vaccine triggers an IgG increase. Tr. 32. The viral RNA in the flu vaccine has been shown to stimulate ANCA production, which is seen in Pauci-immune type of RPGN; the ANCAs trigger neutrophils, which cause kidney damage. Tr. 32-33. While acknowledging that RPGN/PGNMID

[31] Tanu Duggal et al., *Antineutrophil Cytoplasmic Antibody Vasculitis Associated with Influenza Vaccination*, 38 AM. J. NEPHROL. 174-78 (2013), filed as "Pet. Ex. 22."

is not an ANCA-mediated disease, Dr. Kielstein opined that the viral RNA in the flu vaccine may trigger the immune response in a similar manner. Tr. 33. He submitted a study of ANCA-associated vasculitis ("AAV") associated with flu vaccination to support this comparison. The study documented two patients who developed AAV two weeks and four weeks after flu vaccination; the authors also noted, "There are 6 previous cases of AAV in the literature described in temporal association with administration of influenza vaccines." Pet. Ex. 22 at 1. The authors concluded that the flu vaccine "may be a triggering factor" for AAV based on the temporal relationship between vaccination and onset, and also considered molecular mimicry as a possible mechanism, noting that "[t]he influenza antigen and vaccine proteins share substantial structural similarity." *Id*. at 3.

Dr. Kielstein conceded that there is no literature specifically addressing an association between flu vaccine and RPGN/PGNMID but since PGNMID is a new entity, cases are probably underreported. Tr. 25-26, 74-75. Dr. Kielstein added that PGNMID may also be overlooked due to difficulty detecting monoclonal IgG deposits seen only in about 1% of all renal biopsies.[32] Tr. 25-26. Further, the stain for IgG is rarely ordered because the treatment for RPGN and PGNMID is the same, plasma exchange. Tr. 71-73, 77-79; Pet. Ex. 45.[33] Still further, Dr. Kielstein noted that responses to immune stimuli can be difficult to predict, "[s]o we may know exactly what the mechanism is, but we are aware of many diseases where the immune response to a trigger can vary quite considerably." Tr. 78-79. Dr. Kielstein submitted several articles showing other immune-mediated renal disorders occurring following flu vaccine. *See, e.g.*, Pet. Ex. 34[34] (case report of patient who developed acute renal failure and minimal change disease 18 days after flu vaccination); Pet. Ex. 36[35] (case report of patient who developed abrupt-onset nephrotic syndrome and severe acute kidney injury two weeks after an H1N1 flu vaccination); Pet. Ex. 37[36] (case report of patient who developed membranous GN 20 days after H1N1 flu vaccination); Pet. Ex. 38[37] (case report of patient who developed minimal change nephrotic syndrome four days after flu

[32] Dr. Kielstein noted that a pediatric paper whose authors he could not recall examined a large number of renal biopsy samples and found that 0.74% of samples had monoclonal IgG deposits that were not picked up due to the wrong stain being used. Tr. 26.

[33] Naoki Haruyama et al., *Subclinical Nephrosclerosis is Linked to Left Ventricular Hypertrophy Independent of Classical Atherogenic Factors*, 37 HYPERTENS. RES. 472-77 (2014), filed as "Pet. Ex. 45."

[34] Silvina Gutierrez et al., *Minimal Change Disease Following Influenza Vaccination and Acute Renal Failure: Just a Coincidence?* 32 NEFROLOGIA 414-15 (2012), filed as "Pet. Ex. 34."

[35] Chinmay Patel and Hitesh H. Shah, *Membranous Nephropathy and Severe Acute Kidney Injury Following Influenza Vaccination*, 26 SAUDI J. KIDNEY DIS. TRANSPL. 1289-93 (2015), filed as "Pet. Ex. 36."

[36] Ali Kutlucan et al., *Can Influenza H1N1 Vaccination Lead to the Membranous Glomerulonephritis?*, 55 INDIAN J. PATHOL. MICROBIOL. 239-41 (2012), filed as "Pet. Ex. 37."

[37] J.T. Kielstein et al., *Minimal Change Nephrotic Syndrome in a 65-Year-Old Patient Following Influenza Vaccination*, 54 CLIN. NEPHROL. 246-48 (2000), filed as "Pet. Ex. 38."

vaccination); Pet. Ex. 42[38] (case report of patient who had a relapse of minimal change disease after flu vaccination).

In contrast, respondent argued that Dr. Kielstein lacked evidence for his theory, pointing to Dr. Kielstein's acknowledgments of the lack of medical literature associating flu vaccine and RPGN/PGNMID. *See, e.g.*, Tr. 29 ("Well, of course I'm not able to state a specific pathway" for how the flu vaccine could cause RPGN), 31 ("…we have much less evidence and substance to confirm" a pathway between flu vaccine and RPGN similar to the pathway between flu vaccine and GBS), 39 (admitting that there is "scarce evidence" to support a connection between the flu vaccine and RPGN), 70 (agreeing that there are no case reports linking flu vaccine to PGNMID).

Dr. Kaplan "remain[ed] unconvinced" that the flu vaccine could cause PGNMID. Tr. 118. His position was rooted in an overall objection to the notion that vaccines could cause/induce/trigger an autoimmune renal disorder. According to Dr. Kaplan, the prevalence of minimal change nephrotic syndrome has "remained relatively static over time" despite the enormous increase in vaccine administration over the past 50 years. Tr. 118-19. Therefore, there exists "negative epidemiological evidence against there being an association" between flu vaccine and PGNMID. Tr. 119. However, Dr. Kaplan admitted, "I do not rule out the possibility that there could be idiosyncratic cases, in other words, unique cases. But…given the fact that so many vaccines are being administered, you really would expect to see more reports than there are…there has been no report of a single case [of PGNMID] in which there was antecedent vaccination." Tr. 119. Later, Dr. Kaplan conceded, "I didn't say there were no cases of glomerulonephritis allegedly caused by the vaccine. There have been reports." Tr. 124-25.

When discussing the science underlying Dr. Kielstein's theory, Dr. Kaplan appeared to agree with Dr. Kielstein on several key points. Dr. Kaplan agreed that RPGN is mediated by antibody or cellular immunity. Resp. Ex. L at 5. He further agreed that deposition of antibodies along the basement membrane and/or glomerular deposition of preformed soluble immune complexes can result in glomerulonephritis. *Id*. Dr. Kaplan stated, "Antibody- and cell-mediated immunity are together responsible for many lesions observed in patients with acute RPGN, and cell-mediated immunity without antibody (sic) may produce crescentic glomerulonephritis." *Id*. He also agreed that vaccines cause an increase in cytokine and antibody levels. *See* Tr. 116-17 ("…there's no doubt that there are changes in T-cells and so on induced by vaccines").

However, Dr. Kaplan maintained that there was no evidence that the flu vaccine has been implicated in either the antibody-mediated or cell-mediated pathways. Resp. Ex. L at 5. Dr. Kaplan dismissed Nasr's proposition that PGNMID could arise in the course of a normal immune response referring to the proposition as "pure speculation" and not "proof of pathogenesis." Resp. Ex. Q at 2. Dr. Kaplan added that the pathogenesis of PGNMID remains elusive even ten years after the Nasr paper was first published. Tr. 74. Dr. Kaplan rejected the Jeffs paper relied on by Dr. Kielstein, which discussed ANCA vasculitis following flu vaccine, suggesting it to was "pure speculation." Tr. 120. According to Dr. Kaplan, ANCA-associated idiopathic or primary crescentic glomerulonephritis is associated with small vessel vasculitis ("SVV") and may be renal limited or

[38] Olusola Isikalu, Ruth C. Campbell, & Roberto Pisoni, *Minimal Change Disease Relapse after Influenza Vaccination*, 28 J. AM. SOC. NEPHROL. 1134 (2017), filed as "Pet. Ex. 42."

part of a systemic disease such as granulomatosis with polyangiitis, or microscopic polyangiitis and therefore a different disease. Resp. Ex. L at 4; Resp. Ex. Q at 5.

The lack of any literature directly associating PGNMID following flu vaccine was the real sticking point for Dr. Kaplan. Although he agreed with Dr. Kielstein that published evidence supports timing of onset for an immune response to the flu vaccine, Dr. Kaplan opined that the literature does not support a relationship between the flu vaccine and RPGN. Resp. Ex. Q at 1-2; Pet. Ex. 23 at 3[39] (finding that immune response to flu vaccination peaked for some IgM, IgG, and IgA anti-influenza titers seven days after vaccination). Dr. Kaplan noted that "there is not a single case report…in which acute glomerulonephritis or crescentic glomerulonephritis, has been reported following influenza vaccine administration." Resp. Ex. L at 4. Dr. Kaplan also rejected case reports of other kidney disorders following flu vaccine, stating, "[T]he few reported cases with an alleged association between influenza vaccine and various completely different types of glomerular disease, none of which share known common pathogenic mechanisms, do not offer a plausible connection between the vaccination and the coincidental renal disease." Resp. Ex. Q at 4-5.

Dr. Kaplan further disagreed with Dr. Kielstein's analogy of GBS associated with flu vaccine, stating that he was "deeply disturbed" by the acceptance of flu vaccine as a cause of GBS. Tr. 120. Later, when it was pointed out that GBS following flu vaccine was an on-Table injury in the Vaccine Program, Dr. Kaplan backpedaled, stating, "Maybe it's a bit dramatic to say that I was deeply disturbed… if there is more likelihood than not that the vaccine has been shown to be causative, that's fine. Experts have decided that and good people have made that decision. That's fine with me." Tr. 153-54.

Dr. Kielstein responded to Dr. Kaplan's criticisms, stating that, if there were clear-cut evidence that the flu vaccine could trigger RPGN/PGNMID, a hearing would not be necessary in this case. In Dr. Kielstein's opinion, there is in general "an understudied and ill-defined connection between an immune stimulus caused by a vaccine and a renal injury." Tr. 80-81.

In summary, the experts agree that PGNMID is a newly discovered disease and that PGNMID/RPGN is immune-mediated. They agree that the flu vaccine causes activation of B- and T-cells and that the flu virus and viral infections generally can cause immune-mediated renal diseases. The experts disagree on whether the flu vaccine can cause PGNMID and/or RPGN because, as Dr. Kaplan noted, none of the literature has specifically addressed PGNMID/RPGN and influenza vaccine.

It is not unusual in Vaccine Program cases for literature to be sparse. It is also not shocking or unexpected that very little literature exists on PGNMID in general, or its association with influenza virus, influenza vaccine or any vaccine. However, it is not the petitioner's burden to show scientific certainty, nor is literature associating the subject vaccine with the specific injury required. Petitioner must show a scientifically sound and reliable theory, which Dr. Kielstein has done in this matter. Dr. Kielstein provided medical literature illustrating that PGNMID arises in the course of an immune response through activation of B cells, T cells, and IgG, specifically IgG3,

[39] A. Warmold L. van den Wall Bake et al., *Humoral Immune Response to Influenza Vaccination in Patients with Primary Immunoglobulin A Nephropathy*, 84 J. CLIN. INVEST. 1070-75 (1989), filed as "Pet. Ex. 23."

which is intrinsically nephritogenic. *See* Pet. Ex. 26; Pet. Ex. 27. He also submitted literature suggesting that a reaction to viral RNA in the flu vaccine could lead to ANCA-associated vasculitis, also an immune-mediated disorder. *See* Pet. Ex. 29. He further provided case studies of patients who developed immune-mediated renal disorders after receiving flu vaccinations. *See, e.g.*, Pet. Ex. 22; Pet. Ex. 34; Pet. Ex. 36; Pet. Ex. 37; Pet. Ex. 38; Pet. Ex. 42.

Dr. Kaplan's criticisms were more about the lack of literature supporting Dr. Kielstein's theory than the theory itself. He did not disagree that the flu vaccine could cause PGNMID, and in fact agreed that there have been reports of glomerulonephritis allegedly caused by the vaccine. Tr. 124-25. Therefore, by Dr. Kaplan's own admission, the lack of literature does not negate Dr. Kielstein's theory. It was, after all, Dr. Kaplan who described the greatest accomplishments of his career starting with case reports and a theory that led to discoveries of biological evidence supporting the association of medication and/or diseases in the body infiltrating the kidney and causing GN. Essentially, in this case, Dr. Kaplan is suggesting a higher standard of proof be applied, that of scientific certainty, which is not required by the Vaccine Program. *See Andreu*, 569 F.3d at 1378 (Finding that conclusive evidence in medical literature is not required for a causation in fact claim).

Accordingly, I find that petitioner has provided a sound and reliable theory that viral RNA in the flu vaccine can trigger increased IgG and production of cytokines, causing rapid deposition of immune complexes in the glomeruli, damaging the glomerular basement membrane, and resulting in RPGN/PGNMID, an immune mediated disease. Petitioner has satisfied Prong I.

2. Petitioner Has Demonstrated a Logical Sequence of Cause and Effect Connecting the Flu Vaccine to Her Development of RPGN/PGNMID.

Despite some equivocation, Dr. Kaplan ultimately agreed that petitioner suffered from RPGN/PGNMID. *See* Pet. Ex. 21 at 7-8; Resp. Ex. L at 4; Resp. Ex. Q at 6; Resp. Ex. S at 3; Resp. Post-Hearing Brief at 2 ("Dr. Kaplan agreed with this PGNMID classification."), citing Tr. 109-10 ("…they said this condition is proliferative glomerulonephritis with monoclonal IgG deposits. That's what I would have called her"). However, while Dr. Kielstein opined that petitioner suffered from an acute RPGN, Dr. Kaplan initially posited that petitioner had chronic silent kidney disease prior to the allegedly causal flu vaccination, based on petitioner's biopsy results and her 2016 relapse which coincidentally flared after her flu vaccination.

a. Petitioner's treating physicians associated her development of RPGN/PGNMID with her flu vaccine.

As the Federal Circuit noted in *Capizzano*, treating physicians are likely to be in the best position to determine whether "a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." 440 F.3d at 1326. Dr. Carey, a nephrologist who began treating petitioner on November 10, 2011, associated her disease onset with the flu vaccine. *See* Pet. Ex. 2 at 107 (notation in petitioner's medical records that "the flu vaccine may have been the stimulus for the rapidly progressive crescentic GN"). Dr. Carey later authored an affidavit in which he stated, "It is further my opinion that the administration of the influenza vaccination on November 3, 2011 triggered Ms. Isaacson's glomerulonephritis…." Pet. Ex. 14 at 8. Dr. Carey recommended

that petitioner not receive any additional vaccinations "due to the potential harm they pose given her damaged kidneys." *Id*. In Dr. Carey's opinion, "there is no reasonable alternative causation…of the cause of Ms. Isaacson's crescentic glomerulonephritis…." *Id*. at 10. Dr. Taft, who also treated petitioner during her initial hospitalization, noted, "This is a young lady who is experiencing any (sic) glomerulonephritis following an influenza vaccine. Temporally, the two have to be related." Pet. Ex. 2 at 138. Dr. Greene, who treated petitioner at the Mayo Clinic after her 2016 relapse, noted that it was "certainly within the realm of possibility with acute antibody formation" that petitioner's flu vaccine "caused her acute crescentic GN." Pet. Ex. 20 at 5.

b. Dr. Kielstein maintained that the flu vaccine was the cause of petitioner's immune-mediated RPGN and disagreed that petitioner had any evidence of chronic silent kidney disease prior to the November 3, 2011 vaccination.

Dr. Kielstein testified that petitioner's clinical course was consistent with an acute kidney injury from the flu vaccination on November 3, 2011, which resulted in the development of RPGN five days later. Tr. 36-37. He stated in hindsight "it is easy to say" that petitioner's complaints of headache and flu-like symptoms on November 6, 2011 were symptoms of RPGN but conceded there is a "considerable overlap" between the general side effects from flu vaccine and the symptoms associated with RPGN. Tr. 37, 83. However, Dr. Kielstein pointed to petitioner's creatinine level of 3.0 and hematuria, and proteinuria on November 8, 2011, as signs of "overt renal disease that…was not existent prior to vaccination." Tr. 37. She also had an increase in weight, from 190 pounds to 204 pounds, and she had an increase in blood pressure, from 115/70 to 171/94 between November 8 and November 10, 2011, which are "in line with an acute renal disease like RPGN," not a reaction to a flu vaccine. Pet. Ex. 21 at 12. He further noted that other possible causes of RPGN such as lupus, ANCA vasculitis, and post-streptococcal glomerulonephritis were ruled out. Tr. 61. Although it is impossible to rule out everything, petitioner's work up was "very thorough" and excluded 95% of the known causes of RPGN. Tr. 61-62.

Dr. Kielstein noted petitioner's history of urinary tract infections as noncontributory, explaining that UTIs do not ascend into the kidney; they occur in the lower urinary tract. Tr. 63. In order to affect the kidneys, petitioner would have to have frequent severe upper UTIs, which she did not. Tr. 63. Dr. Kielstein explained that frequent UTIs can result in interstitial scarring, but he believed the interstitial findings on petitioner's biopsy was the result of ciprofloxacin, which petitioner was prescribed. Tr. 63-64. Ciprofloxacin can cause abnormalities in the interstitium but does not cause RPGN. Tr. 64.

Further, Dr. Kielstein pointed out that petitioner had none of the characteristics of chronic renal disease prior to vaccine such as hypertension, elevated creatinine, or proteinuria, even during pregnancy, which is often "a trigger mechanism for making silent renal disease…become visible." Tr. 39-40. Furthermore, Dr. Kielstein postured that petitioner's kidney biopsy was not consistent with pre-existing kidney disease, even though it showed two sclerotic glomeruli.

Dr. Kielstein explained that longstanding hypertension[40] can cause renal disease and sclerosed glomeruli on biopsy. Pet. Ex. 21 at 11. But, petitioner's blood pressure and echocardiogram[41] were normal in January of 2013. *See* Pet. Ex. 2 at 694-96. If she had long-term hypertension, the ECHO would have shown changes to the left ventricle due to the need for muscle power. Tr. 46-47, 49-50; Pet. Ex. 21 at 11; Pet. Ex. 45 at 1[42] (finding that a high percentage of global glomerulosclerosis was significantly associated with left ventricular hypertrophy). When petitioner reported to the ER on November 8, her blood pressure was normal. Two days later, on November 10, she had "full-blown hypertension" a typical clinical sign of RPGN.

Further, Dr. Kielstein noted that petitioner did not have increased blood pressure even during pregnancy, when blood pressure is known to increase. Tr. 46-47; Pet. Ex. 47 at 116, 136, 201; Pet. Ex. 50 at 1. She had a higher blood pressure on only two occasions, in May and December of 2010; the December blood pressure reading was taken on the day she gave birth, when high blood pressure is expected. Tr. 48; Pet. Ex. 47 at 136. There are no medical records indicating that petitioner had preexisting hypertension, even during pregnancy. Tr. 48-49, 64.

Dr. Kielstein further noted that petitioner did not have proteinuria, or protein in her urine, in the year prior to her flu vaccine and development of RPGN/PGNMID. He explained that chronic kidney disease is characterized by two components: one, an impairment in renal excretory function, which is a decreased ability of the kidney to get rid of toxins, and two, disturbance of the glomerular barrier function, which results in protein or blood in the urine. Tr. 51. The two can occur separately. Tr. 51. "You can have normal excretory renal function…but at the same time have signs of renal damage detected by detecting either blood or protein in the urine…." Tr. 51. A healthy kidney does not let albumin, a protein, pass through the blood into the urine. Tr. 51. Petitioner's urine albumin was regularly measured during her pregnancy and was consistently negative. Tr. 50; Pet. Ex. 47 at 201.

Dr. Kielstein acknowledged there is no record of petitioner's creatinine levels prior to vaccination, but petitioner's excretory renal function was normal, and she returned to normal after the November 2011 episode of severe kidney injury, which makes it unlikely that she had impaired renal function prior to the vaccination. Tr. 51-52. "You don't start with 50 percent renal function, get additional damage and go back to 100 percent renal function. That's not possible." Tr. 52.

Dr. Kielstein added that ultrasound images of petitioner's kidneys do not show pre-existing kidney disease. An abdominal ultrasound on November 10, 2011, showed that petitioner's kidney size was "well above the age adjusted median" for 30-year-old subjects. Pet. Ex. 21 at 11-12; Pet.

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[40] According to Dr. Kielstein, for a person of petitioner's age, it would take blood pressure readings of 170-180 mm/Hg over a period of five years to cause damage. Tr. 49.

[41] An echocardiogram is a record of the position and motion of the heart walls or the internal structures of the heart and surrounding tissue. *Echocardiogram*, DORLAND'S at 583; *echocardiography*, *id*.

[42] Naoki Haruyama et al., *Subclinical Nephrosclerosis is Linked to Left Ventricular Hypertrophy Independent of Classical Atherogenic Factors*, 73 HYPERTENS. RES. 472-77 (2014), filed as "Pet. Ex. 45."

Ex. 2 at 360; Pet. Ex. 31 at 5.[43] A follow-up ultrasound on December 14, 2011, showed that her kidneys had returned to normal size. *Id*. at 12; Pet. Ex. 2 at 253. An ultrasound on January 21, 2012 also showed the kidneys at normal size, with no evidence of renal mass, hydronephrosis, or renal calculi. *Id*.; Pet. Ex. 2 at 251. In contrast, if petitioner had long standing kidney disease, there would be severe sclerosis on ultrasound, the kidneys would appear shrunken, and the surface would not be very smooth. Tr. 49-50. In comparing the various ultrasounds, Dr. Kielstein opined that petitioner had "considerable acute swelling of the kidneys [on November 10, 2011] that on follow-up examination did not exist anymore." Pet. Ex. 21 at 12.

Dr. Kielstein discussed the findings on the kidney biopsy taken seven days after the administration of the flu vaccine which documented "an acute inflammatory process involving eight out of nine glomeruli with glomerular crescents, fibrinoid necrosis, acute renal tubular injury, acute interstitial changes, and glomerular immune deposits." Pet. Ex. 21 at 8. Two of nine glomeruli were globally sclerotic.[44] *Id*. Dr. Kielstein emphasized that "[f]ive of the non-globally sclerotic glomeruli had *fresh*, circumferential cellular crescents," with no mention of old crescents, "strongly suggesting that the injury is acute and not chronic." *Id*. at 8, 11 (emphasis in original).

In addressing the two sclerotic glomeruli found on the biopsy, Dr. Kielstein explained that renal diseases are divided into nephrotic, nephritic, and sclerotic categories; "sclerotic" means there are scarred glomeruli, attributed to high blood pressure over a long period of time. Tr. 40. He referred to the Kremers article, which studied over 2000 healthy individual kidney donors and found an age dependent increase in sclerotic glomeruli. Tr. 40; Pet. Ex. 30[45] (examining the number of globally sclerotic glomeruli across multiple age groups to distinguish age-related glomerulosclerosis from disease-related glomerulosclerosis). In 18- to 29-year-olds with nine to 16 glomeruli on biopsy, one globally sclerotic glomerulus is considered normal. Pet. Ex. 21 at 11; Pet. Ex. 30 at 4. Dr. Kielstein opined that in this case the two sclerosed glomeruli did not demonstrate proof of pre-existing renal disease, because the number of sclerosed glomeruli can change within the location of the kidney, "[s]o you could have a sampling error [where] you have more sclerosed glomeruli in certain regions of the kidney." Tr. 43. Further, the sample of nine glomeruli in this case was insufficient to circumvent a sampling error; 15 to 20 glomeruli would have been a better sample. Finally, the exact location of where the biopsy was taken from was not documented in the report in this case. Tr. 41-43; Pet. Ex. 21 at 9, 11. According to Dr. Kielstein an insufficient sample means you must weigh a small sample size against the diagnostic conclusions you are making, here given the context of the biopsy results, "…even having two sclerotic glomeruli out of nine is…no (sic) convincing evidence of preexisting renal disease. Tr. 41-42.

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[43] Sarah Faubel et al., *Renal Relevant Radiology: Use of Ultrasonography in Patients with AKI*, 9 CLIN. J. AM. SOC. NEPHROL. 382-94 (2014), filed as "Pet. Ex. 31."

[44] Dr. Kielstein explained that sometimes, the sclerosis, or scar, does not affected the whole glomerulus. Tr. 41. When the whole glomerulus is affected by scarring, it is referred to as "globally sclerotic." Tr. 41.

[45] Walter K. Kremers et al., *Distinguishing Age-Related From Disease-Related Glomerulosclerosis on Kidney Biopsy: the Aging Kidney Anatomy Study*, 30 NEPHROL. DIAL. TRANSPLANT. 2034-39 (2015), filed as "Pet. Ex. 30."

Dr. Kielstein further submitted that the pathology report did not describe glomerulosclerosis with a pattern of solidification or focal segmental glomerulosclerosis, which would also be consistent with kidney disease rather than normal aging. Pet. Ex. 41 at 3. None of the other factors used to determine degree of chronicity in renal biopsies – tubular atrophy, interstitial fibrosis and arteriosclerosis – were described in the histology report for petitioner in November of 2011. *Id*.; Pet. Ex. 44.[46] Dr. Kielstein concluded, "The clinical condition that led to the sclerosis of two glomeruli in the renal biopsy…is more likely than not aging and not arterial hypertension." *Id*. at 4; Tr. 40, 64-66.

Dr. Kielstein added that biopsy results should be examined in the context of the clinical picture and petitioner's clinical course. The histological findings were not typical for this disease. Tr. 42; Pet. Ex. 21 at 9. Clinical data associated with PGNMID showed only 12.5% of patients with this disease have complete remission. Pet. Ex. 27 at 6. The patients in complete remission had fewer than three percent of glomeruli with crescents, and those with partial remission had fewer than twenty percent of glomeruli with crescents. *Id*. at 7. In contrast, petitioner had five out of seven (71%) glomeruli with crescents. Tr. 42; Pet. Ex. 41 at 4-5; Pet. Ex. 21 at 9. The fact that petitioner was able to regain normal excretory renal function with treatment was surprising and fortunate and further proof that she did not have chronic kidney disease. Tr. 42.

Dr. Kielstein noted if he were to look at the biopsy results alone, with so many glomeruli affected, he would have suggested petitioner was facing a lifelong decrease of renal function. Tr. 42. He believes this was the reason petitioner's doctors ordered five plasma exchange procedures. Tr. 42. However, petitioner had a "dramatic" recovery after only two treatments, and her doctors were "able to revert this acute occurring illness in a very short period of time." Tr. 42. Petitioner's remarkable renal recovery was due to the acute nature of her disease. Pet. Ex. 21 at 9. A person who had underlying renal disease and then experienced acute RPGN would have a very low chance of recovering normal renal function. Tr. 44. When the biopsy results are viewed in the context of petitioner's dramatic recovery and other test results, it is more likely that petitioner was within the normal range of sclerotic glomeruli as part of aging and did not have preexisting renal disease. Tr. 43-44.

Finally, Dr. Kielstein pointed out that viral infections and infections of the upper respiratory tract can trigger a relapse of RPGN and accounts for petitioner's relapse in January of 2016. Tr. 53. Dr. Kielstein pointed out that petitioner's nephrologist, Dr. Carey, documented her relapse in January of 2016 as preceded by a "viral illness, again." Pet. Ex. 41 at 6; Pet. Ex. 40 at 9. When petitioner was admitted for her relapse, she reported that her daughter had a viral illness, and Dr. Carey subsequently concluded that this episode of GN was triggered by viral illness. Pet. Ex. 41 at 6; Pet. Ex. 40 at 382.

c. According to Dr. Kaplan, petitioner developed flu-like symptoms following the flu vaccine, a coincidental flare of her silent chronic renal disease as evidenced by the biopsy results, and a relapse in January of 2016 further supporting that she had chronic renal disease.

[46] Musab S. Hommos et al., *Global Glomerulosclerosis with Nephrotic Syndrome; the Clinical Importance of Age Adjustment*, 93 KIDNEY INT. 1175-82 (2018), filed as "Pet. Ex. 44."

In Dr. Kaplan's opinion, petitioner "developed a flu-like illness with emesis, fevers, chills, myalgias, neck pain, and headache three days after receiving the influenza vaccine," and coincidentally, suffered from a preexisting renal disease, which flared following her receipt of the flu vaccination. Resp. Ex. L at 3, 8. Dr. Kaplan submitted that petitioner's biopsy showed changes indicative of a chronic condition and her relapse in January 2016 solidified that she suffered from an underlying chronic renal disease. The influenza vaccine played no role in her renal illness.

According to Dr. Kaplan, petitioner did not present with "the usual clinical signs and symptoms of an acute glomerulonephritis; specifically, there was no evidence of edema, hypertension, gross hematuria, oliguria or anuria." Resp. Ex. L at 3; Tr. 131. Over 50% of patients with crescentic glomerulonephritis present with acute nephritic syndrome, characterized by hematuria, proteinuria, oliguria, edema, and hypertension, and rapidly deteriorating renal function. *Id*. at 5. Another 10% of patients may have nephrotic syndrome, characterized by edema, massive proteinuria, severe hypoalbuminemia, and hyperlipidemia; 15% of patients present with chronic renal failure. *Id*. However, 15% of patients may be asymptomatic and petitioner was among the 15% who are asymptomatic and whose diagnosis is made for other reasons. *Id*.

According to Dr. Kaplan, petitioner's complaints of "emesis, fevers, chills, myalgias, neck pain, and headache" were "a well-known side of the vaccine and [were] not in any way related to her nephrology issues." Resp. Ex. L at 3. Since she had a "complete absence of any renal symptoms that are usually associated with an acute glomerulonephritis of any type," it is "probable that her renal disease may not have been diagnosed when it was, had she not had symptoms from the influenza vaccine." *Id*. at 5.

Dr. Kaplan agreed with Dr. Kielstein that the ultrasound findings of enlarged kidneys support petitioner having had an acute illness, and that the subsequent renal ultrasound showed recovery from the acute illness. Resp. Ex. Q at 4. However, Dr. Kaplan opined, this does not negate the evidence of chronic as well as acute kidney injury on the biopsy. *Id*.

According to Dr. Kaplan, the biopsy in November of 2011 showed evidence of both acute and chronic damage. Specifically, there was evidence of "an acute inflammatory process with glomerular crescents, fibrinoid necrosis, acute renal tubular injury, acute interstitial changes and glomerular immune deposits." Resp. Ex. L at 3; Resp. Ex. Q at 2. There was "evidence of chronic glomerular injury [global sclerosis, segmental glomerular sclerosis] and chronic interstitial injury [chronic interstitial fibrosis]" which, "more than likely not" predated the vaccine and flu-like symptoms. *Id*. According to Dr. Kaplan, sclerotic glomerular and/or interstitial changes occur over weeks or months after an initial acute injury; they are indications of a healing process analogous to scarring after inflammation or surgical injuries. *Id*. These chronic findings were an indication of a "silent" underlying kidney disease predating petitioner's vaccination and subsequent flu-like symptoms. *Id*.

Dr. Kaplan agreed that petitioner did not have tubular atrophy or arteriolosclerosis, which are also features of chronic disease. Resp. Ex. S at 1-2. However, in his opinion, the lack of arteriosclerosis is less significant than the other findings that do indicate chronic changes, i.e., global sclerosis, focal segmental sclerosis, and chronic interstitial fibrosis. *Id*., citing to Pet. Ex.

43 at 3[47] ("Lesser weight is attached to arteriosclerosis compared with GS [glomerulosclerosis] and IFTA [interstitial fibrosis tubular atrophy] because both GS and IFTA have been found to be predictors of poor renal outcomes…whereas such prediction is much less consistently found with arteriosclerosis.").

In further support of his opinion that the biopsy showed features of both acute and chronic kidney disease, Dr. Kaplan pointed to the various degrees of sclerosis evident on petitioner's biopsy. He explained that five of the glomeruli on the first biopsy had "fresh" crescents which are crescents that are cellular and have not undergone fibrosis or sclerosis. Tr. 137. Old crescents have undergone fibrosis and begin to constrict the glomeruli; this suffocates the blood supply to the glomeruli, causing glomeruli death. Tr. 137. If petitioner's biopsy showed crescents, proliferative changes, and an increased number of cells without any fibrosis, "I would have said that she has an acute injury and there is no chronic component to it. But that was not the case on the first biopsy." Tr. 137.

Further, Dr. Kaplan stated the biopsy contained four sclerotic glomeruli, two of which demonstrated global sclerosis. *See* Pet. Ex. 4 at 332-33. Dr. Kaplan agreed with Dr. Kielstein that a certain amount of sclerotic tissue is an acceptable part of the aging process and would be located under the capsule of the kidney. Tr. 101-02. He also agreed that it is unknown where the biopsy was taken from, in relation to the capsule of the kidney in this case. Tr. 100-02. However, he added that the study on age-related sclerosis Dr. Kielstein relied upon found an upper limit of one globally sclerotic glomerulus on biopsy to be appropriate for ages 18 to 29. Resp. Ex. Q at 3, citing Pet. Ex. 30 at 4.

Dr. Kaplan stated that, if petitioner had only two globally sclerotic glomeruli on biopsy, "I would have no case to make that the vaccine was unlikely to be implicated in the disease." Tr. 102. But petitioner had two glomeruli with focal segmental sclerosis, which means part, but not all, of the glomerulus was scarred. Tr. 102. At two different times during the hearing, Dr. Kaplan testified that the focal sclerosis was significant because "it takes at least three weeks for scar formation to occur in the kidney," and "at least three weeks for the glomeruli to become globally sclerosed as well as to develop segmental sclerosis," therefore, "those scars could not have occurred in the short period between the administration of the vaccine and [petitioner's] biopsy." Tr. 103, 138. However, Dr. Kaplan could not recall where this three-week period came from and did not cite to any supporting medical literature for this statement. Tr. 103. He then concluded that, based on this time frame, petitioner's preexisting kidney disease was there months or years prior to vaccination, but he would not know how long. Tr. 138.

Further, Dr. Kaplan postulated that petitioner's 2016 relapse was another indicator of chronic injury and noted that petitioner's symptoms were similar to those at the time of first occurrence with flu-like illness, headache, fever, chills, and myalgias but negative testing for meningitis, flu, or other viruses. Resp. Ex. Q at 3, 5. At hearing, Dr. Kaplan stated that there was no viral infection or vaccine ascribed to her 2016 relapse. When it was pointed out that petitioner's medical records documented a viral infection and fever at the time of her relapse, Dr. Kaplan would not address the possibility that an acute virus caused her relapse; but rather, side-stepped, stating

[47] Sanjeev Sethi et al., *A Proposal for Standardized Grading of Chronic Changes in Native Kidney Biopsy Specimens,* 91 KIDNEY INT. 787-89 (2017), filed as "Pet. Ex. 43."

that would follow his logic that between her first and second episode, whatever condition was causing her kidney disease was still present and available to flare up. Tr. 113.

Dr. Kaplan added that, with the benefit of hindsight, the fact she had a second episode with similar symptoms without a vaccine means that he cannot look at the first episode in isolation. Tr. 143-44. If she only had the first episode, his only argument against vaccine-causation in this case would be that the interval between the vaccine and manifestation of illness was extremely short and there was evidence of chronicity on the first biopsy. Tr. 144. After the second episode, "…it was clear that she had even more chronic changes in her kidney," not only in the glomeruli but also with the findings of interstitial fibrosis, another manifestation of chronicity." Tr. 145-46.

According to Dr. Kaplan, petitioner's February 2016 biopsy showed four globally sclerotic glomeruli; the increased number of globally sclerotic glomeruli indicates that petitioner had an ongoing silent kidney process, despite ostensibly being in remission. Tr. 106. "…[A]nybody looking at her second biopsy where there were four sclerotic glomeruli, they would have said [petitioner] has an underlying chronic illness." Tr. 137. These findings, Dr. Kaplan maintained, supported a pre-existing or "subclinical renal disease" based on biopsy findings. Tr. 104.

Further, in his second report, Dr. Kaplan maintained that petitioner developed hypertension after her initial episode of RPGN. The combination of hypertension along with abnormal increased 24-hour urine protein excretion on three occasions, April 25, 2016, August 24, 2016, and November 3, 2016, and increased urine albumin excretion on May 16, 2017, indicated that she had chronic renal injury. Resp. Ex. Q at 4. However, petitioner's medical records reflect that she maintained normal blood pressures following her initial episode RPGN without medication.[48] At hearing, Dr. Kaplan conceded that petitioner did not have long-term hypertension, nor was that the cause of the chronic and preexisting kidney disease he believed petitioner had. Tr. 131. He qualified that he was not suggesting that "she walked around with manifestations of kidney disease all the time," but that she had injury to her kidney prior to her presentation of symptoms. Tr. 136. She was not in chronic renal failure; if she was, her creatinine "would never have gone down to normal" after the first episode. Tr. 136. But Dr. Kaplan maintained that, just because she recovered well from immunosuppressive therapy after both episodes, does not rule out that she had chronic kidney disease, as everyone responds differently to treatment. Tr. 134-36.

[48] Petitioner was initially prescribed lisinopril on December 13, 2011 due to a blood pressure of 144/72 at nephrology appointment. Pet. Ex. 4 at 306-07. On December 16, 2011, petitioner telephoned Dr. Carey to report that she had not taken the lisinopril. *Id.* at 307. She attributed her high blood pressure reading to nervousness and advised that she had been monitoring her blood pressure at work with normal readings. *Id.* Dr. Carey advised petitioner to "hold" the lisinopril and continue monitoring her blood pressure. *Id.* At subsequent appointments, petitioner had the following blood pressures: 136/84 on December 28, 2011; 122/76 on January 31, 2012; 123/70 on May 1, 2012; 123/60 on July 2, 2012; 116/70 on August 13, 2012; 117/76 on October 8, 2012; 122/70 on October 26, 2012; 117/68 on January 7, 2013, at which time petitioner was pregnant; 130/70 on June 3, 2013, at which time petitioner was 35 weeks pregnant; 120/86 on August 13, 2013; 131/84 on September 10, 2013; 125/54 on September 19, 2013; 113/83 on December 3, 2013; 110/68 on June 9, 2014; and 116/74 on August 7, 2014. *See* Pet. Ex. 4 at 2, 5, 267, 288, 345-46; Pet. Ex. 5 at 5, 8, 11, 14, 17, 21, 61; Pet. Ex. 10 at 4, 79. Petitioner was not noted to have "mildly elevated" or "borderline" blood pressures until after her relapse in 2016. *See* Pet. Ex. 40 at 20, 25, 36, 41.

I asked Dr. Kaplan if his opinion was that petitioner had an ongoing chronic condition that manifested itself for the first time five days after her vaccine, as opposed to a condition caused by the vaccine and if so, why no other doctor that was involved in her treatment, whether pathologist or nephrologist, concluded that she had an ongoing chronic condition? Dr. Kaplan responded, "Well, I think you have summed up my position really well" and her subsequent episode added weight to the theory that she had a condition capable of manifesting itself again. Tr. 110-11. Many patients with nephrotic syndrome or glomerulonephritis present with a constellation of flu-like symptoms, even in the absence of any known infectious cause. Tr. 111-12. Dr. Kaplan did not provide a response as to why none of petitioner's treating physicians at any of the facilities where she was treated concluded that she had a chronic condition.

Dr. Kaplan added that one can have a pre-existing asymptomatic kidney disease and not know it. Tr. 154. When asked whether it was possible for the flu vaccine to trigger a pre-existing but silent kidney disease, Dr. Kaplan responded, "That's the essence of this case, Special Master. That's what you are going to decide." Tr. 154.

d. The evidence herein supports an acute onset of RPGN/PGNMID following influenza vaccination and lends little support for a chronic silent renal disease.

For the most part, the experts herein agree petitioner had RPGN/PGNMID but disagree on whether petitioner's kidney disease was, at the time of the influenza vaccine, acute or longstanding. Dr. Kielstein contends that all the evidence supports an acute immune-mediated disease of PGNMID following the receipt of an influenza vaccine on November 3, 2011. The findings of sclerotic tissue on the biopsy were age-related, not disease related. Dr. Kaplan ultimately agreed that petitioner presented with an acute onset of PGNMID but opined that the biopsy findings also supported a silent, but long-standing chronic disease evidenced by focal glomerulosclerosis similar to what develops after an injury and which takes months develop.

At hearing, it appeared at times that Dr. Kaplan was saying petitioner had long-standing chronic silent kidney disease that coincidentally flared along with her suffering from typical side effects associated with the flu vaccine and at other times that she suffered an acute RPGN as well as having long standing chronic silent kidney disease. He further conflated the findings of the second biopsy in 2016 with the biopsy of November 2011, stating that it was the first biopsy that showed focally sclerotic glomeruli and sclerotic tissue indicative of long-standing disease. Tr. 102-04. However, it was the renal biopsy performed on February 3, 2016, not November of 2011 which showed 14 glomeruli, four of which were globally sclerotic and five crescents with two other glomeruli showing focal necrotizing areas and moderate tubular atrophy with mild interstitial fibrosis involving about 15% of the interstitial compartment. Pet. Ex. 40 at 550-51. Petitioner's doctors in January of 2016 concluded that this biopsy was "consistent with the crescentic form of proliferative glomerulonephritis with monoclonal IgG deposits…This would represent a recurrence." *Id*. at 550. "It was felt that her viral illness triggered this episode of GN." *Id*. at 382.

Dr. Kaplan maintained that petitioner's second episode over four years later confirmed his theory of chronic disease because she had the same onset of symptoms in the absence of infection or vaccination. Tr. 111, 128-29. This too was not accurate. When petitioner presented to the

hospital on January 31, 2016, she reported becoming ill with fever, chills, body aches, and nausea following her daughter's viral illness a few days prior. Her symptoms worsened and she presented with a fever of 100.4 degrees and labs which showed an elevated white blood cell count. She was admitted to the hospital with sepsis. Her doctors documented, "It was felt that her viral illness triggered this episode of GN." Pet. Ex. 40 at 382; Pet. Ex. 20 at 11.

The key differences in the experts' opinions lie in their interpretation of the reported findings on the biopsies. But the treating physicians' opinions are more in line with petitioner's expert, Dr. Kielstein. At the risk of belaboring the point, the biopsy taken on November 11, 2011 showed crescentic glomerulonephritis, immune complex-type. *See* Pet. Ex. 2 at 531 ("This patient has diffuse extra capillary proliferative glomerulonephritis (crescentic glomerulonephritis). The presence of IgG Kappa predominance by IF is suggestive of a new glomerular entity termed proliferative glomerulonephritis monoclonal IgG Kappa"). Of the nine glomeruli in the biopsy sample, two were globally sclerotic, two showed segmental sclerosis, and five non-globally sclerotic glomeruli contained fresh and cellular crescents, almost all of which were circumferential. Pet. Ex. 2 at 532. The second biopsy, performed on February 3, 2016, showed "proliferative crescentic GN with positive immunofluorescence." Pet. Ex. 40 at 382. Further, a nephropathology report dated April 21, 2016 from the Mayo Clinic compared petitioner's biopsies from November 2011 and February 2016 and concluded that she had proliferative glomerulonephritis with monoclonal IgG kappa deposits with necrotizing and crescentic activity and minimal chronicity. Pet. Ex. 20 at 11-12. There was no mention of chronic kidney disease only the characteristics of an immune mediated GN, now known as PGNMID.

Dr. Kaplan postulated, "[A]nybody looking at her second biopsy where there were four sclerotic glomeruli, they would have said [petitioner] has an underlying chronic illness." Tr. 137. However, this was not the case. Petitioner's biopsy results were noted to have "fresh" crescents and "acute" findings. None of the biopsies were interpreted by any nephrologist or pathologist as showing a chronic long-standing kidney disease.

Dr. Kielstein countered Dr. Kaplan's view of chronic but silent kidney disease, pointing out that petitioner had no hypertension or proteinuria, not even during pregnancy, when a silent kidney disease would likely flare. He also addressed her prior urinary tract infections, pointing out that lower urinary tract infections would not affect the kidneys unless they were severe and ascended into the upper urinary tract which the record does not indicate occurred. Dr. Kielstein explained that the interstitial findings on biopsy could have been the result of ciprofloxacin, which petitioner was prescribed. Most importantly, Dr. Kielstein pointed out that petitioner recovered to 100% renal function, which could not happen if she had preexisting kidney disease. This was borne out in her recurrence in January of 2016 from which she did not recover completely.

Both experts in this case were knowledgeable, candid, with a great deal of respect shown for one another. Dr. Kielstein conceded what he did not know and focused on what he did know and what was supportable. He stated that he took every effort to provide the exact explanation in a pathophysiological way. Tr. 62. He hoped with future research there would be a more thorough understanding to identify the few who would be at risk for severe side effects of a vaccination, concluding, "I think that on that background, I'm really able to elucidate pathophysiological mechanisms that then could help to identify a subject at risk." Tr. 62-63.

Dr. Kaplan also conceded and agreed where appropriate. His digressions were informative. As set forth above, his own experiences show the value of reporting experiences in medicine as case studies when encountering rare events. Over his 50 years of practice, Dr. Kaplan made associations between events occurring in his practice and kidney disease. He admitted PGNMID has only recently been discovered as a separate and identifiable immune-mediated GN and ultimately agreed that was the condition petitioner should be diagnosed with. He agreed with the acute nature of the onset of her disease and that she did not have a history of hypertension, even during pregnancy. He agreed that elevated creatinine cannot determine chronic versus acute kidney disease, that petitioner presented with elevated creatinine that went back to normal after immunosuppressant therapy, and that the ultrasounds before and after treatment showed enlarged and normal kidneys, respectively. He did not dispute Dr. Kielstein's statement that someone with acute renal failure like petitioner experienced would not have returned to normal function rapidly after treatment if there were a silent chronic kidney disease present.

Ultimately, to satisfy my inquiry on Prong II, I asked Dr. Kaplan if he would agree that the potential exists for the flu vaccine to have played a role in petitioner's kidney disease, even if it did not cause it. Dr. Kaplan responded, "I would have to do somersaults to get out of that question the way you put it… So I still have my doubts that the flu vaccine actually triggered it. I don't know that it didn't." Tr. 155.

Accordingly, petitioner has sustained her burden under Prong II.

3. Petitioner Has Shown an Appropriate Temporal Relationship Between Her Receipt of Flu Vaccine and Her Development of Acute Glomerulonephritis.

Dr. Kielstein opined that petitioner's onset of symptoms three to five days post-vaccination was an appropriate temporal interval for an autoimmune reaction. Dr. Kaplan disagreed; in his opinion, a three-day onset was too short for an autoimmune reaction. Additionally, Dr. Kaplan submitted that petitioner's symptoms on November 6, 2011, were not consistent with a renal condition or glomerulonephritis, and the timing of petitioner's diagnosis of RPGN seven days after her flu vaccination was coincidental.

According to Dr. Kielstein, published literature supports "the onset of renal side effects of influenza vaccination that have been based on renal biopsy findings, have been described 4 days (Ex. 38) to 4 weeks (Ex. 22) after the vaccination." Pet. Ex. 21 at 8. Dr. Kaplan agreed with Dr. Kielstein, going so far as to state, "It is gratifying to me that Dr. Kielstein agrees with me" on the timing of onset for an immune response to flu vaccination. Resp. Ex. S at 1; *see also* Resp. Ex. Q at 1-2 (agreeing that "published evidence…supports the notion" that an immune response to flu vaccination occurs within four days to four weeks of vaccination).

To further support his opinion, Dr. Kielstein pointed out that the package insert for the flu vaccine lists side effects in terms of severity for the first seven days "because this is the timeframe for an intense immune response." Tr. 82. As set forth above, "on day seven, you have a peak in the immunoglobulin production and side effects. Especially those that can be attributed to the cytokine production are predominantly found within the first seven days." Tr. 82.

Petitioner testified that three days after her November 3, 2011 flu vaccine, she began to experience "headache, body aches, [and] typical viral symptoms." Tr. 10. On November 7, 2011, she developed severe chills and neck pain and was unable to get out of bed to go to work. Tr. 10-11. This was unusual and as a nurse, alarming. Tr. 10-11. She presented to the hospital on November 8, 2011. At that time, five days after vaccination, her creatinine was elevated at 3.0. Tr. 37-38.

Dr. Kielstein explained how a severe autoimmune injury like RPGN could occur within five days of vaccination. "…you have the cytokine changes within hours of the vaccination and you have the antibiotic [sic] production peaking on day seven but of course ramping up much earlier. So from a theoretical point of view, that timeframe would be sufficient enough to – for the vaccine causing RPGN." Tr. 37.

Specifically, petitioner had a creatinine level of 3.0 on November 8, five days after vaccination, which "means the onset of the renal disease had to be prior to that…it would probably [take] like two days to get your creatinine up from 1 to 3 with full-blow inflammation of the kidney. So [onset] had to be between day three and five." Tr. 38. In other words, for petitioner's creatinine to be at 3.0 when she went to the ER on November 8, 2011, the immune process must have begun three to five days before. Tr. 37-38. Dr. Kielstein cited to several articles of medical literature to support his opinion. *See, e.g.*, Pet. Ex. 38 (case report of patient who developed minimal change nephrotic syndrome four days after flu vaccination); Pet. Ex. 22 (study noting eight patients who developed ANCA-associated vasculitis between 12 days and four weeks after flu vaccination); Pet. Ex. 23 at 3 (finding that immune response to flu vaccination peaked for some IgM, IgG, and IgA anti-influenza titers seven days after vaccination).

However, at hearing, Dr. Kaplan stated that petitioner's onset of symptoms *three days* post-vaccination was not medically appropriate. In his opinion, three days is "not even at the short end of the time intervals that people have shown for known immunological causes of renal injury." Tr. 126. For example, glomerulonephritis caused by *streptococcus* bacteria usually occurs within seven to 14 days of infection. Tr. 126. According to Dr. Kaplan, looking at all of the immunologically mediated forms of kidney disease in which a pathogen has more likely than not been found to have a relationship with glomerulonephritis, there are no examples where the onset is as short as three days. Tr. 127.

Dr. Kaplan subsequently opined that petitioner's onset of symptoms *four days* post-vaccination was an outlier when compared to the cases discussed in Pet. Ex. 22, where eight patients developed ANCA-associated vasculitis between 12 days and four weeks after flu vaccination. Tr. 127-28; Pet. Ex. 22 at 4. This contrast added to Dr. Kaplan's doubts that petitioner's RPGN/PGNMID was associated with the flu vaccine. Tr. 128. However, he then conceded that there was a case where a patient had onset of minimal-change nephrotic syndrome within four days of flu vaccination. Tr. 149; Pet. Ex. 38.

In response to Dr. Kielstein's opinion that petitioner's creatinine level of 3.0 on November 8 indicated that her immune process started three to five days before, Dr. Kaplan stated that petitioner's creatinine level on the day of her flu vaccination was unknown, so it is unclear how many days it would take for her creatinine level to increase to 3.0. Tr. 99, 138. He added that

doubling time of serum creatinine depends on the disease involved; some say it is between 1.0 and 1.5 milligrams a day. Tr. 99. It could take years for a person's creatinine level to increase from normal to 3.0, depending on the underlying condition. Tr. 138-39. No literature was provided in support of this testimony.

In his reports, Dr. Kaplan agreed with Dr. Kielstein that an immune response to the flu vaccine can occur within four days to four weeks of vaccination. At hearing, he placed petitioner's onset of symptoms at both three days and four days post-vaccination. Even when he placed onset at four days, within the range that he previously agreed was appropriate, he refused to accept that petitioner's onset of symptoms could be consistent with an immune response to the flu vaccine.

Dr. Kielstein persuasively explained that cytokine changes occur within hours of vaccination, peaking with an immune response seven days post-vaccination. He cited to studies, and case reports to support this opinion. He then explained how petitioner's clinical course comports with a severe autoimmune response to the flu vaccine. Petitioner suffered normal side effects initially after the flu vaccine. Then, four days after vaccination, she developed neck pain and an inability to get out of bed. Five days after her flu vaccine, petitioner presented to the ER; she had a creatinine level 3.0. On November 10, 2011, petitioner returned to the ER in complete renal failure and was hospitalized. The kidney biopsy performed on November 11, 2011, seven days after vaccination revealed acute crescentic GN, with fresh crescents, breaks in the glomerular basement, and evidence of IgG immune complexes, consistent with the literature for RPGN/PGNMID. Having had flu vaccines in the past, petitioner's rapid onset of an immune-mediated disease within three to four days of a vaccination is well-supported by relevant medical literature.

Petitioner has satisfied Prong III.

C. Burden Shifting: Respondent Must Show an Alternative Cause of Injury

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Human Servs*., 98 Fed. Cl. 719 (2011). Consequently, the burden now shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *De Bazan*, 539 F.3d at 1354; *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe/11 v. Sec'y of Health & Human Servs.*, 83 Fed. Cl. 157 (2008) (holding that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

Respondent submitted that petitioner had a preexisting chronic silent kidney disease. His position through his expert evolved from the initial preexisting silent kidney disease which the flu vaccine had nothing to do with to an acute and chronic kidney disease that Dr. Kaplan could not say was not affected by the influenza vaccine. Respondent's position is not persuasive.

Based on the foregoing, I conclude that the influenza vaccine petitioner received on November 3, 2011 was the cause of or a substantial contributing factor in causing her RPGN/PGMNID.

VI. Conclusion

Petitioner has presented preponderant evidence that the influenza vaccine she received on November 3, 2011 was the significant factor in her development of RPGN/PGMNID. This case shall proceed to damages.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master